REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-9, 13, and 15-19 will be pending in the application subsequent to entry of this Amendment.

The claims have been amended in order to more particularly point out and distinctly claim that which applicants regard as their invention, to address various issues raised in the outstanding Official Action and to advance prosecution generally. The claims directed to compounds have been revised to state a compound in the singular, claims 10-12 and 14 have been deleted in order to advance examination and "use of ..." claims 16-18 have been recast as in method format. New claim 19 has been added; *see* page 4, second full paragraph of the description and compare with page 2, item 4, second sentence of the Official Action.

The issues raised in the outstanding Official Action are addressed below in the order presented:

4. Claims 14-18 – 35 U.S.C. § 112 paragraph 1 (enablement)

The applicants duly considered this objection, but they cannot agree with it.

Camptothecins are a well-known class of antitumor drugs used for the treatment of different tumors. The description of the invention makes explicit reference to EP 1 044 977 (EP '977), of record and the literature cited therein. This reference reports that camptothecins demonstrated a wide spectrum of antitumor activity, in particular against colon tumors, other solid tumors and leukemias (see page 1, fourth paragraph). The clinical reference for camptothecins is Topotecan, which is indicated for the treatment of small and non-small cell lung, ovarian, breast, stomach, liver, prostatae, soft tissue sarcoma, head and neck, oesophagus, resistant colon-rectum, multiform glioblastoma, chronic and acute myelocytic leukemias (EP'977, page 3, third paragraph). The compounds disclosed in EP'977, of which the compounds of the present invention are derivatives as far as the 7-$C(R_5)$=N-O-R_4 substituent is concerned, and the activity on a wide range of tumors is proved by the enclosed list of references retrieved from PubMed (ENCLOSURE 1). See also Penco et al., US 6,242,457 (of record), claiming priority of EP'744, where the range of treated tumors was expanded (column 14).

Further evidence of a wide range of antitumor activity is found in the same references cited by the examiner, see WO 97/00876, page 23, third full paragraph.

Therefore, the state of the art should be fully taken into account, since there is no reason to believe that the claimed compounds are not effective on different tumors. To the contrary, the problem solved by the present invention is to enhance stability of the molecule, thus enhancing the pharmacological activity gives a person skilled in the art a more powerful therapeutic tool.

The present compounds are not claimed for treating tumors which are not usually treated with Topoisomerase I inhibitors or with camptothecins in general. This is very clear from the whole content of the description and the references cited therein. Therefore, the skilled reader will know for which type of tumors the compounds can be used.

Activity of camptothecins in parasitic and viral infections is well-known in the art (see WO'876, page 23, first full paragraph).

In view of the above, applicants respectfully request withdrawal of this rejection.

6. Claims 1-18 – 35 USC §112, paragraph 2 (claim clarity)

Amended claim 1 is corrected above with the correct formula (I) inserted in place of the previous one. The editing error is evident from the content of the description, in particular see page 10, synthesis scheme, Examples and list of preferred compounds. Nothing more than camptothecin derivatives was originally intended by the applicants and this correction offered is to adjust the claim and clarify the record.

The Reformatsky reaction is a well-known method for lengthening the carbon chain of carboxylic acids, a page from a university organic chemistry handbook is enclosed (ENCLOSURE 2) to confirm this.

Claim 7 has been corrected and applicants thank the Examiner for pointing out the error.

Claim 12 has been deleted, thus rendering the objection moot.

Claim 14 has been deleted, thus rendering the objection moot.

Claim 15 is maintained but amended to depend from claim 13. Applicants believe this claim is clear to the skilled reader, since combining different antitumor drugs is common knowledge and practice in this field. The other antitumor drug will be determined by the skilled clinician simply exercising his or her knowledge.

Claims 17 and 18 are maintained, since applicants believe that the skilled person will know how to use the invention just resorting to common knowledge. A sample of relevant literature is enclosed (ENCLOSURE 3).

8. Claims 11 and 16-18 – 35 U.S.C. § 101

Claim 11 is deleted as being non-statutory.

Claims 16-18 have been amended and cast as method claims. Claim 19 is added and is directed to specify a type of tumor.

9.-10. Claims 1-3, 6, 7 and 12-18 – 35 U.S.C. § 102(b)

Claim 1 has been further amended by introducing a proviso to disclaim compounds specifically disclosed by Bigg et al.

Claim 10 has been deleted, thus rendering the objection moot.

13. Claims 1-4 and 12-18 – 35 U.S.C. § 103(a) – Penco in view of Bom

Applicants acknowledge the cited references are relevant to the above claims. However, the cited references do not lead the skilled person to the claimed invention for at least the following reasons.

Bom et al. disclose camptothecins having modified lactone ring, but the characteristic feature of Bom et al. compounds is the substituent in position 7, which is a silyl derivative. The Bom et al. teaching is limited to this feature, since the title of their work, Bom et al. declare that lipophilicity is the essential characteristic of their camptothecin derivatives (Novel A,B,E-Ring-Modified Camptothecins Displaying High Lipophilicity and Markedly Improved Human Blood Stabilities – emphasis added).

The primary reference, Penco et al., provided a new class of camptothecin derivatives, which are camptothecin 7-substituted oximes. These compounds were successfully patented notwithstanding the technical prejudice existing in the art at that time that camptothecin activity was proportional to the lipophilic character of the 7-substituent (Penco et al., col. 4, lines 32-51, in particular lines 49-50). The technical prejudice was represented by the authoritative Sawada et

al. paper cited in the passage mentioned here; this paper refers back to US 4,399,276, cited both in Penco et al. and in the present circumstance of this application.

The Bom et al. paper was published in 1999, the same year of Penco et al's priority date. This indicates that Bom et al. were not aware of Penco et al's patent (published in 2001), but were aware of Sawada US'276 (published in 1983) thus they plainly followed the state of the art teaching to provide highly lipophilic substituent in position 7 of camptothecin skeleton.

Penco et al. are not concerned with the problem of stabilizing the lactone ring, but rather in the problem of low water solubility, gastrointestinal and bone marrow side effects, resistance against topoisomerase I inhibitors by certain tumor lines and how to improve therapeutic index (column 3, last paragraph to column 4, line 1).

Penco et al. fully succeeded in improving therapeutic index (column 4, lines 62-64; column 13) and water solubility (column 13, lines 31, injectable formulations).

The skilled person will understand that the modification at position 7 with a lower lipophilic group, such as a substituted oxime (the same as in the present compounds) enhances therapeutic index through the increase of the persistence of DNA cleavage stimulated by camptothecins and mediated by topoisomerase I (see column 13, lines 35-67).

Bom et al. note an antitumor activity which is not much better than that of camptothecin, one of the less effective compounds of this family due to very low water solubility (Penco et al., column 1, lines 17-28). This comparison is not very significant, since the best Bom et al compound DB-38 is worse than camptothecin; see the corresponding WO 00/61146, page 55, cited in the present application together with the Bom et al's paper cited by the Examiner. In any case, the increase (?) of activity is explained with the improved stability of the lactone ring.

The person skilled in the art, with the problem of improving stability of Penco et al.'s camptothecins will find in Bom et al. the indication that lactone ring can be expanded in highly lipophilic camptothecins (bearing a highly lipophilic substituent in position 7).

The person skilled in the art knows that the lipophilicity-lowering modification made by Penco et al. to lipophilic camptothecins of Sawada (US'276) improves antitumor activity by enhancing persistence of DNA cleavage stimulated by camptothecins and mediated by topoisomerase I.

This person also knows that antitumor activity is at least maintained (not increased) in camptothecins substituted in position 7 with a highly lipophilic group by enlarging the lactone ring from 6 to 7 members in order to increase plasma stability.

It is evident that the two teachings do not agree with each other. Penco et al. teach how to improve the intracellular phenomenon of DNA cleavage, whereas Bom et al. teach to improve plasma stability.

There is no indication that applying Bom et al.'s teaching to Penco et al.'s the goal of still achieving a better therapeutic index would be met (present application, page 3, second paragraph). To the contrary, it does not seem that the improved plasma stability achieved by Bom et al. increases antitumor activity.

Quite surprisingly, the present invention provides compounds with extremely higher activity (see page 15, Table 1). Therefore, there is no teaching at all in Bom et al. that the lactone ring modification barely maintaining antitumor activity with respect to a well-known poorly effective compound (camptothecin) would provide a campthotecin derivative with increased activity.

Applicants respectfully request acknowledgment of non obviousness of the claimed subject-matter and withdrawal of the objection.

14. Claims 1-4 and 12-18 – 35 U.S.C. § 103(a) – Dallavalle

Dallavalle et al. is not available as prior art thus cannot be considered in the examination of the present invention. Dallavalle et al. bears a publication date of June 2002, but likely made available to the public even later.

The present application enjoys a priority date of May 31, 2002, clearly before Dallavalle et al. was published.

Applicants respectfully request withdrawal of the rejection.

For the above reasons it is respectfully submitted that the claims of this application define inventive subject matter. Reconsideration and allowance are solicited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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ENCLOSURE 1

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Gimatecan, a novel camptothecin with a promising preclinical profile.

Pratesi G, Beretta GL, Zunino F.

Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy. graziella.pratesi@istitutotumori.mi.it

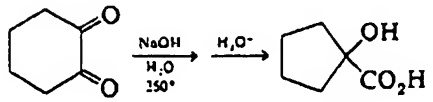
The realization that position 7 of camptothecin allows several options in chemical manipulation of the drug has stimulated a systematic investigation of a variety of substituents in this position. These efforts resulted in the identification of a novel series of 7-oxyiminomethyl derivatives. Among compounds of this series we have selected a promising lipophilic derivative, gimatecan, for further development. The relevant features of gimatecan are: (i) marked cytotoxic potency, likely related to multiple factors, including a potent inhibition of topoisomerase I, a persistent stabilization of the cleavable complex, an increased intracellular accumulation and a peculiar subcellular localization; (ii) lack of recognition by known resistance-related transport systems; (iii) increased lactone stability and favorable pharmacokinetics; (iv) good oral bioavailability; and (v) an impressive antitumor efficacy in a large panel of human tumor xenografts, with various treatment schedules. Phase I clinical studies with oral administration support the preclinical results of the novel camptothecin. Using different schedules and dosing durations, gimatecan exhibited an acceptable toxicity profile, with myelotoxicity being the dose-limiting toxic effect. An appreciable number of tumor responses was achieved and favorable pharmacokinetics with a very long terminal half-life was observed. The clinical development of gimatecan is currently ongoing, with phase II studies in diverse tumor types (colon, lung, breast carcinoma and pediatric tumors).

Publication Types:
- Review

PMID: 15205595 [PubMed - indexed for MEDLINE]

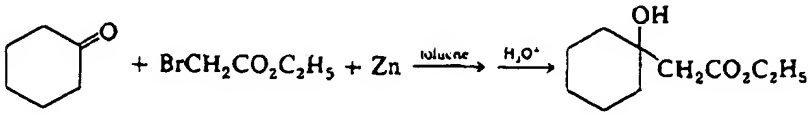
ENCLOSURE 2

When the α-diketone is cyclic, the rearrangement serves as a method of ring contraction.

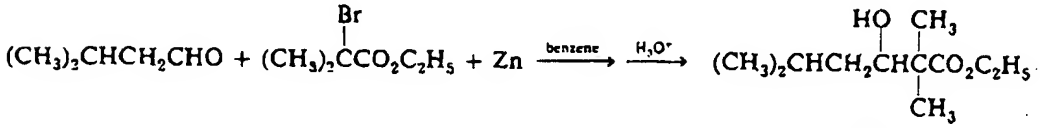


(80%)

4. THE REFORMATSKY REACTION. β-Hydroxy esters result when an aldehyde or a ketone is treated with an α-halo ester and zinc in an inert solvent (the Reformatsky reaction).

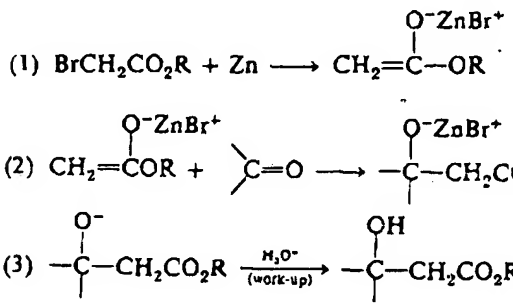


(70%)
ethyl (1-hydroxy-cyclohexyl)acetate

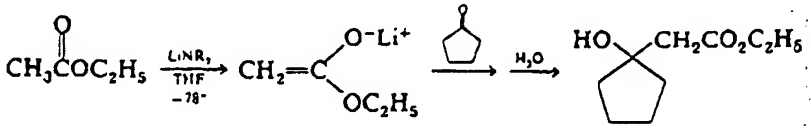


(65%)
ethyl 2,2,5-trimethyl-3-hydroxyhexanoate

The reactive intermediate in the Reformatsky reaction is an organozinc reagent that may be regarded as the anion of an ester (Section 18.8), closely associated with a zinc cation. This carbanion has nucleophilic properties and undergoes addition to the carbonyl group of the aldehyde or ketone.

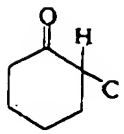


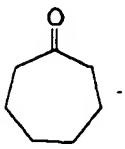
A more recent version of the same reaction utilizes the lithium enolate of an ester, which is prepared by treating the ester with a lithium dialkylamide (Section 18.8). Addition of an aldehyde or ketone gives the β-hydroxy ester in good yield.



(93%)

5. HYDROLYSIS OF LACTONES. Various hydroxy acids are available by the hydrolysis of lactones, which may be obtained by the Baeyer-Villiger oxidation of cyclic ketones (Section 15.8.A).





B. React

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